

# Role of Leukotriene in Gastric Ulcer Induced by Acetyl Salicylic Acid in Male Rabbits : Gastroprotection by Montelukast

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## Abstract

Gastric mucosal damage is a common disorder of the gastrointestinal system. Non-steroidal anti-inflammatory drugs (NSAID) are known to be aggressive agents for gastric ulcer development. Leukotrienes play an important role in gastric mucosal damage induced by NSAIDs. Montelukast, a selective reversible Cysteinyl leukotriene receptor 1 antagonist, was reported to have beneficial effects in management of experimental gastric mucosal ulceration. This study designed to evaluate the role of leukotriene against acetyl salicylic acid-induced gastric mucosal damage and to evaluate the gastroprotective activity of montelukast. Thirty local domestic male rabbits had been used in this study, divided into five groups as follows: normal control group, acetylsalicylic acid (ASA) treated group, Omeprazole pretreatment group, montelukast pretreatment group, montelukast alone treatment group. At the end of the experiment, the stomach of rabbit is removed to prepare the tissue homogenate. The results revealed that after administration of ASA significantly increase the mean ulcer index along with the LTD4 concentration, LTB4 concentration. But in presence of montelukast there is a significant decreased in the mean ulcer index along with LTD4 concentration, LTB4 concentration. These results suggest that the leukotrienes play an important role in acetyl salicylic acid induced gastric ulcerations and gastroprotective activity of montelukast can be attributed to decreased activity of leukotrienes in gastric mucosa.

**Keywords :** Gastric ulcer, *H. pylori*, Non-steroidal anti-inflammatory drugs, montelukast

## 1. Introduction

Gastric ulcer is one of the most common diseases in the world, which affects approximately 5–10% of people during their lives. It is an erosion of the gastric mucosal layer or excavation of the surface of gastric tissue as a result of the sloughing of inflammatory necrotic tissue (Yuan *et al.*, 2006). It develops because of imbalance between aggressive factors (acid, pepsin, *H. pylori*, bile salts) and defensive (cytoprotective) factors (mucous, bicarbonate, blood flow, epithelial cell restoration and prostaglandins) (Zhu *et al.*, 2008).

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs worldwide and their beneficial therapeutic properties are thoroughly accepted. However, they are also associated with gastrointestinal (GI) adverse events including gastric mucosal erosions, ulcerations, bleeding, and perforation (Sostres *et al.*, 2013). NSAID's are known as one of the most common pathogenic factors associated with gastric ulcer (Konturek, 2003).

Acetylsalicylic acid (Aspirin, ASA), is one of the NSAID which is widely used for the treatment of rheumatoid arthritis and related diseases as well as the prevention of cardiovascular thrombotic diseases (Heibashy *et al.*, 2014). It damages gastrointestinal mucosa by two mechanisms: (i) by direct local injury and (ii) by systemic inhibition of cyclo-oxygenase resulting in a relative deficiency of prostaglandins. (Wallace, 2001).

There is an indication that COX inhibition by NSAIDs enhanced synthesis of leukotrienes that occur by shunting the arachidonic acid metabolism towards the 5-lipoxygenase pathway (Hudson *et al.*, 1993; Martel-Pelletier *et al.*, 2003). Leukotrienes (LTs), derivatives of arachidonic acid are synthesized in response to cell activation from membrane phospholipids. Cysteinyl leukotrienes (CysLTs), namely LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub>, are potent proinflammatory lipid mediators produced from arachidonic acid through 5-lipoxygenase (5-LOX) pathway (Hedi and Norbert, 2004). LTB<sub>4</sub> are important modulators of various neutrophils functions including adherence and chemotaxis (Damtew *et al.*, 1993). Leukotrienes are supposed to contribute to gastric mucosal injury by promoting tissue ischaemia and inflammation (Peskar, 1991; Martel-Pelletier *et al.*, 2003; Gandhi *et al.*, 2012). It has been reported that bioactive metabolites of LTs have an essential role in oxidative stress (Sener *et al.*, 2007).

Montelukast, a selective reversible Cysteinyl leukotriene receptor 1 antagonist, is used in the treatment of allergic rhinitis and asthma (Benninger and Waters, 2009). Montelukast was reported to have beneficial effects in management of experimental gastric mucosal ulceration (Sener *et al.*, 2005; Dengiz *et al.*, 2007).

**The aim of study :** To evaluate the role of leukotriene against acetyl salicylic acid-induced gastric mucosal damage and to evaluate the gastroprotective activity of montelukast.

## 2. Materials and methods

### 2.1 Drug

Acetyl salicylic acid was obtained in the form of powder from schuchardt Company, Germany. Montelukast was obtained in the form of tablet from MSD Company, United Kingdom. Omeprazole vial obtained from Cipla Company, India.

### 2.2 Experimental Animals

Thirty local domestic male rabbits had been used in this study; their weight was between (1.5 to 2.5) kg. The rabbits were fed with standard chow diet and they had free access to drink water.

### 2.3 Induction of Gastric lesion

Induction of gastric lesion was carried out on rabbits administered acetylsalicylic acid (ASA) which is given orally through a stomach tube in a dose of 500 mg/kg body weight (b.w.) as single dose (Debnath and Guha, 2007).

### 2.4 Experimental Protocol

After two weeks of adaptation period, the animals were randomly separated into 5 groups (6 rabbits in each group). All the animals in group 3, group 4 were pretreated with the tested drugs in a single daily dose of each one for three days as shown:

**Group 1 (Normal control group):** all rabbits in this group were received distilled water (DW) 5 ml orally through stomach tube during an experimental period.

**Group 2 Acetylsalicylic acid (ASA) treated group (active control group):** all rabbits in this group were received acetylsalicylic acid (500 mg/kg b.w.) orally through stomach tube as single dose.

**Group 3 (Omeprazole pretreated group):** all rabbits in this group were received omeprazole (20 mg/kg b.w.) intraperitoneally (i.p) one hour before acetylsalicylic acid administration.

**Group 4 (Montelukast pretreated group):** all rabbits in this group were received montelukast (20 mg/kg b.w.) orally through stomach tube one hour before acetylsalicylic acid administration.

**Group 5 (Montelukast alone treated group):** all rabbits in this group were received montelukast (20 mg/kg b.w.) orally through stomach tube one hour before administration of 5 ml DW.

The tested drugs were continually given for three days, one hour after the last dose (3<sup>rd</sup> day) of thirty six hours fasted animals. ASA was administered orally to the animals (except normal control group and montelukast alone treated group) in a dose of (500 mg/kg b.w.), then all the animals were sacrificed five hours later. All experiments were performed during the same time of the day to avoid diurnal variations of putative regulators of gastric functions.

### 2.5 Preparation of Drugs.

#### 2.5.1 Acetylsalicylic acid (ASA) powder

ASA powder was suspended in distilled water (Lichtenberger *et al.*, 2011) and given orally through stomach tube in a dose of 500 mg/kg according to the protocol described by (Debnath and Guha, 2007).

#### 2.5.2 Omeprazole 40 mg vial:

Omeprazole 40 mg vial (Cipla, B.N V20422) mixed with distilled water and given (i.p) in a dose of 20 mg/kg according to the protocol described by (Prasad *et al.*, 2012).

#### 2.5.3 Montelukast 10 mg tablet.

Montelukast (MSD, B.N 324759) was suspended in distilled water; ten tablets of this drug were crushed and suspended in distilled water to prepare a fresh solution immediately before administration, and used in a dose of 20 mg/kg administered orally through a stomach tube according to the protocol described by (Dengiz *et al.*, 2007).

### 2.6 Collection and Preparation of sample.

At the end of the experiment, the animals were sacrificed by an overdose of chloroform vapors and the stomach was separated from the surrounding viscera then washed with physiological saline solution pH 7.4 to determine the ulcer parameters by means of dissecting microscope (Khalil *et al.*, 2010). Tissue Homogenate was prepared according to method of Hussein *et al.*, 2014 for the determination of the leukotrienes concentration.

### 2.7 Measurement of Different Parameters:

#### 2.7.1 Gastric lesion parameters.

The stomach opened along the greater curvature, washed with normal saline and examined under dissecting microscope to calculate lesions parameters which constitute the following:-

- 1- Total lesion (Long lesions and Petechial lesions) length in (mm) for each stomach was measured and

served as the ulcer index. Each five petechial lesions were taken as 1mm of ulcer . The sum of the total length of long ulcers and petechial lesions in each group of rats was divided by its number to calculate the ulcer index (mm) (Alkofahi and Atta, 1999 ).

- 2- The preventive index ( P.I.) was calculated for each group using the following equation: (Michael *et al.*, 2001) .

$$\text{P.I.} = \frac{\text{U.I. of ASA group} - \text{U.I. of pretreated group}}{\text{U.I. of ASA group}} \times 100$$

**2.7.2 Determination of Gastric Tissue Leukotriene D4 Concentration .** The measurement has been done according to method illustrated by Rabbits leukotriene D4 Kit

**2.7.3 Determination of Gastric Tissue Leukotriene B4 Concentration .** The measurement has been done according to method illustrated by Rabbits leukotriene B4 Kit.

## 2.8 Statistical analysis of data:

The results were expressed as mean  $\pm$  standard deviation (mean  $\pm$  SD). Statistical analysis was carried out using one way ANOVA followed by least significance difference( L.S.D.) test for multiple comparisons between groups by using the 19 edition of SPSS program . A value of  $p < 0.05$  was considered to indicate a significant difference between groups.

## 3. Results

### 3.1. Effect of The Studied Drugs on Gastric Ulcer Index in Male Rabbits.

The administration of acetylsalicylic acid showed a significant increase in ulcer index ( $P < 0.05$ ) ( $34.25 \pm 5.84$  mm ) when compared with the normal control group. While The administration of omeprazole and montelukast showed a significant decrease in ulcer index ( $P < 0.05$ ) ( $2.53 \pm 0.58$  mm ) ( $6.7 \pm 0.37$  mm ) with preventive index 93% , 81% respectively when compared with the acetylsalicylic acid treated group ( $34.25 \pm 5.84$  mm ), table ( 1).

#### Gastric tissue leukotriene D4 concentration .

The administration of acetylsalicylic acid showed a significant increase in gastric tissue leukotriene D4 concentration ( $P < 0.05$ ) ( $27.89 \pm 0.42$  ng/ml ) when compared with the normal control group (  $9.64 \pm 0.58$  ng/ml ), figure ( 2 ) . While the administration of omeprazole and montelukast showed a significant decrease in gastric tissue leukotriene D4 concentration ( $P < 0.05$ ) ( $24.09 \pm 0.26$  ng/ml ) ( $13.53 \pm 0.45$  ng/ml ) respectively when compared with the acetylsalicylic acid treated group .

### 3.2. Gastric tissue leukotriene B4 concentration.

The administration of acetylsalicylic acid showed a significant increase in gastric tissue leukotriene B4 concentration ( $P < 0.05$ ) ( $7.13 \pm 0.66$  ng/ml ) when compared with the normal control group (  $1.74 \pm 0.45$  ng/ml ), figure ( 3 ) . while the administration of omeprazole and montelukast showed a significant decrease in gastric tissue leukotriene B4 concentration ( $P < 0.05$ ) ( $5.97 \pm 0.48$  ng/ml ) ( $3.19 \pm 0.5$  ng/ml ) respectively when compared with the acetylsalicylic acid treated group

## 4. Discussion

The integrity of the gastric mucosa is dependent on a balance between luminal aggressive factors (such as acid and pepsin) and the maintenance of the protective mucosal barrier. Damage to the gastric mucosa results when this balance is disrupted by either an increase in aggressive factors or disruption of the protective gastric mucosal barrier (Prabha *et al.*, 2011 ; Kalra *et al.*, 2011 ).

Acetyl salicylic acid (ASA, aspirin) are widely used with major limitation due to their potentially serious risk of gastrointestinal side effects ranging in severity from mild dyspepsia to gastrointestinal hemorrhage and perforation ( Vonkeman and van de Laar , 2010; Fujimori *et al.* , 2010) .

The finding of the present study after administration of ASA showed a significant increase (  $p < 0.05$  ) in ulcer index in comparison with normal control group and this in agreement with Sener-Muratoglu *et al.*, 2001 who found that ASA induced gastric mucosal lesions in rat model . From the other side, administration of acetylsalicylic acid caused a significant increase (  $p < 0.05$  ) in serum leukotriene D4, leukotriene B4 concentrations in comparison with normal control group. In the same line, Nishio *et al.*, 2007 showed that Cysteinyl leukotriene ( CysLT ) production in the stomach or the small intestine was increased by pretreatment with indomethacin.

There is a number of mechanisms have been suggested to explain the mucosal damage induced by ASA, one of these mechanisms is local direct damage of gastric mucosa (Schlansky and Hwang, 2009 ; Matsui *et al.*, 2011) . ASA acts locally through the release of salicylic acid in the stomach, salicylic acid un ionized in

gastric juice .It enters and accumulates within the epithelial cells of stomach then ionized intracellularly and disturbs cell metabolic functions, increasing mucosal permeability and allowing the back diffusion of H<sup>+</sup> ions (Kauffman, 1989; Papatheodoridis and Archimandritis, 2005) .

Other mechanism has been proposed to explain the gastric mucosal damage induced by ASA related to their ability to inhibit the cyclooxygenase ( COX ) enzyme that is responsible for conversion of arachidonic acid to prostaglandins ( PG) that are needed to keep the gastric mucosal integrity ( Lichtenberger, 2001). However, there is an evidence that COX inhibition by NSAIDs diverting arachidonic acid metabolism to 5-lipoxygenase (5-LOX) pathway, suggests the possible role of leukotrienes (LTs) in gastric mucosal damage through their stimulatory effects on neutrophil adherence to vascular endothelium ( chemotaxis ), affect vascular tone and its effects on vascular permeability promoting vascular stasis and subsequent reduction in tissue perfusion ( Rainsford , 1987; Martel-Pelletier *et al.* , 2003; Gandhi *et al.*, 2012 ) .

According to the results of the present investigation, enhanced generation of 5-lipoxygenase (5-LO) products ( Leukotriene D4, Leukotriene B4) and significant increase in ulcer index of acetylsalicylic acid treated group proved that leukotrienes are involved in gastric mucosal damage .

Recently, many authors have been used Omeprazole as a reference drug for drug screening studies (Takawale *et al.*, 2011; Firdous *et al.*, 2012 ).Omeprazole, a proton pump inhibitor (PPI), exhibits an anti-secretory effect through inhibition of the gastric H<sup>+</sup>/K<sup>+</sup> ATPase at the secretory surface of parietal cell and gastroprotective effect through inhibition of neutrophil functions ( Morjan *et al.*,2013).According to the results of the present investigation, omeprazole significantly decreased gastric ulcer index concomitantly with decreased leukotriene D4 and B4 levels when compared with acetylsalicylic acid treated group this may reflect the gastroprotective activity of omeprazole on gastric mucosa . Okazaki *et al.*, 2007 who found that gastroprotective effects of PPT attributed to the significantly increased PGE2 and decreased LTB4 levels in comparison to the H2-blocker group during the ulcer-healing stage.

According to the results of the present investigation, montelukast significantly decreased the gastric ulcer index concomitantly with decreased gastric leukotriene D4 and B4 levels when compared with acetylsalicylic acid treated group this may reflect the gastroprotective activity of montelukast through inhibition of leukotriene concentration. This finding was in line with that reported by viradia *et al.*, 2011 who investigate the gastro-protective activity of montelukast along with curcumin in rats with aspirin plus pylorus ligation -induced gastric ulcer model . Sener *et al.*,2005 in their study also found that montelukast has gastroprotective activity in alendronate induced lesions of the rat gastric mucosa . Also It was reported by Dengiz *et al.*, 2007 that leukotriene D4-receptor antagonists montelukast ameliorate the indomethacin -induced gastric mucosal damage.

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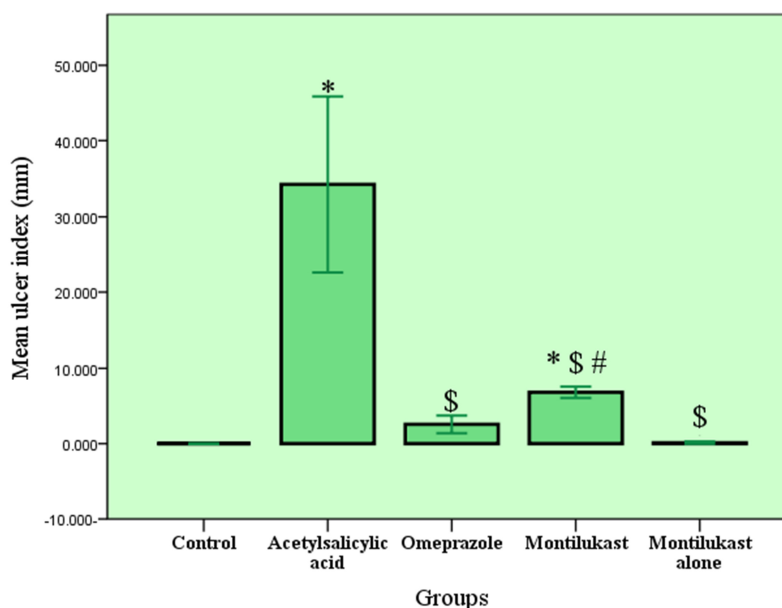
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**Table (1): The effect of the studied drugs on ulcer index in male rabbits.**

Groups	Ulcer index( mm) Mean + SD	preventive index
Normal control group	0	100%
Acetylsalicylic acid treated group	34.25 ± 5.84	0%
Omeprazole pretreated group	2.53 ± 0.58	93%
Montelukast pretreated group	6.7 ± 0.37	81%
Montelukast alone treated group	0.12 ± 0.075	0 %

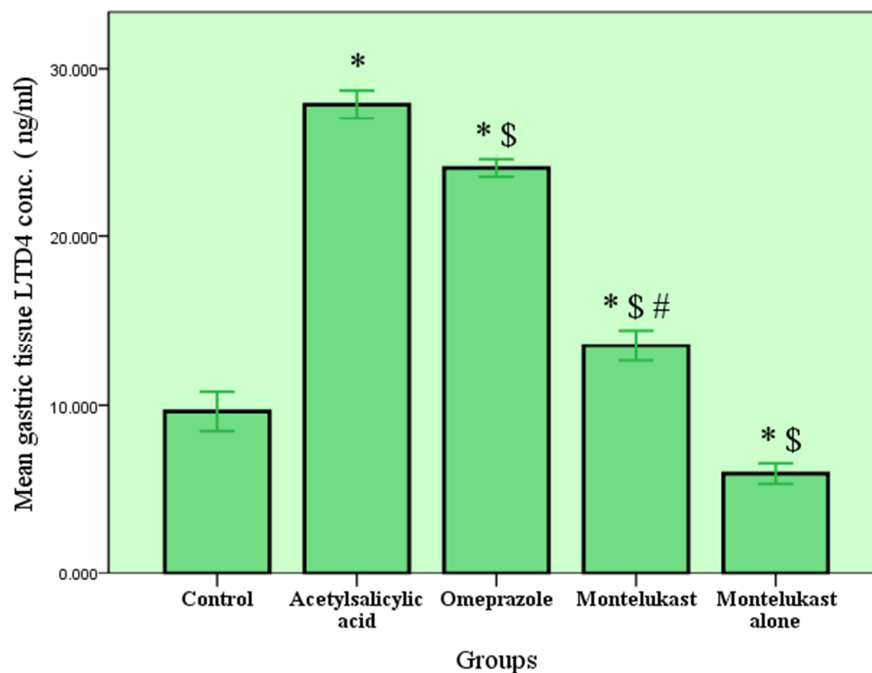


\*: Different Significantly (P<0.05) from normal control group.

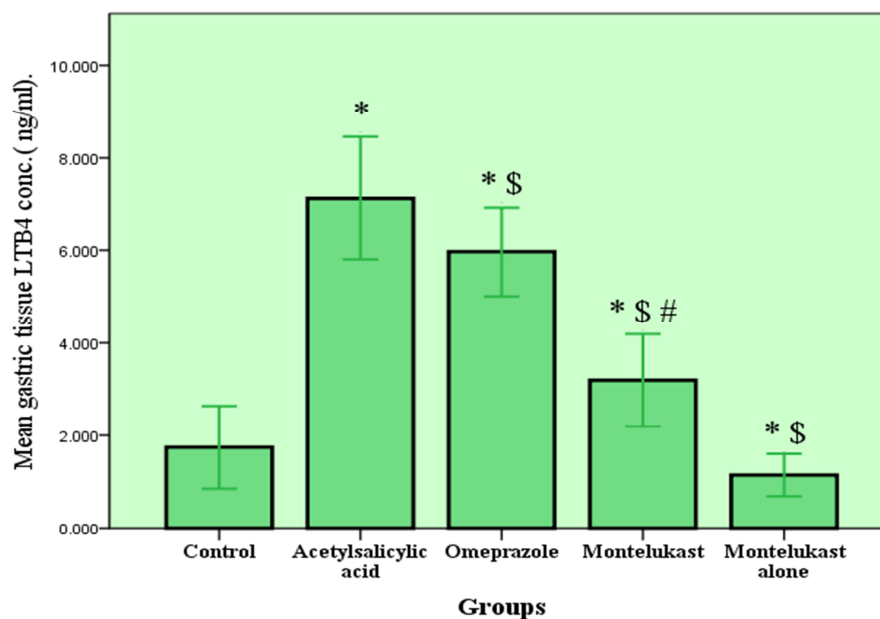
\$ : Different Significantly (P<0.05) from acetylsalicylic acid group.

#: Different Significantly (P<0.05) from omeprazole group.

Figure ( 1 ) : Effect of the studied drugs on gastric ulcer index in male rabbits.



\*: Different Significantly ( $P < 0.05$ ) from normal control group.  
 \$ : Different Significantly ( $P < 0.05$ ) from acetylsalicylic acid group.  
 #: Different Significantly ( $P < 0.05$ ) from omeprazole group  
**Figure ( 2 ) : Effect of the studied drugs on gastric tissue LTD4 concentration.**



\*: Different Significantly ( $P < 0.05$ ) from normal control group.  
 \$ : Different Significantly ( $P < 0.05$ ) from acetylsalicylic acid group.  
 #: Different Significantly ( $P < 0.05$ ) from omeprazole group.  
**Figure ( 3 ) : Effect of the studied drugs on gastric tissue LTB4 concentration .**

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